REMARKS

Claims 32-34, 36, and 39-82 are currently pending in the Application. Applicants note with appreciation that a number of prior rejections have been withdrawn. In the Office Action mailed November 7, 2007, the Examiner raised a number of new rejections. For clarity, these rejections are listed below in the order in which they are addressed herein:

1. Claims 32-34, 36, and 39-82 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite;
2. Claims 32, 34, 35, 37-41, 48-54, 60, 61, 63-65, 72-74, 76, 77, 81 and 82 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ledford, *et al.*, J. Mol. Diagn. 2000 May 2(2):97-104, (hereinafter "Ledford") in view of U.S. Patent No. 5,770,365 to Lane, *et al.*, (hereinafter "Lane") in view of Lau, *et al.*, Science 294:858-862 (2001)(hereinafter "Lau");
3. Claims 33, 36, 44-47, 58, 59, and 62, and 68-71 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ledford, in view of Lane and in view of Lau, further in view of Morris, *et al.*, J. Clin. Microbiol., 1996 Dec., 34(12):2933-6, (hereinafter "Morris");
4. Claims 42, 43, 53, 66, 67, and 77 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ledford in view of Lau and in view of Lane, further in view of Marras, *et al.*, Genet Anal. 1999 Feb., 14(5-6):151-6 (hereinafter "Marras");
5. Claims 55, 56, 79 and 80 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ledford in view of Lau and in view of Lane, in further view of U.S. Patent No. 5,985, 563 to Hyidig-Nielsin, *et al.*, (hereinafter "Hyidig-Nielsin").

The Claims Are Not Indefinite

1. Claims 32-34, 36, and 39-82 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. In particular, asserts that the term "said probe" in step (b) lacks proper antecedent basis. Applicants respectfully disagree. Nonetheless, for business reasons and without acquiescing to the Examiner's arguments, and reserving the right to prosecute the original or similar claims in one or more future applications, Claim 32 is amended herein to recite in step (b) "said unlabeled probe". For consistency, Claim

57 is similarly amended. As such, Applicants submit that these claims meet the requirements of 35 U.S.C. § 112, second paragraph, and respectfully request that these rejections be removed.

The Claims Are Not Obvious

2. Claims 32, 34, 35, 37-41, 48-54, 60, 61, 63-65, 72-74, 76, 77, 81 and 82 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ledford, *et al.*, J. Mol. Diagn. 2000 May 2(2):97-104, hereinafter "Ledford" in view of U.S. Patent No. 5,770,365 to Lane, *et al.*, (hereinafter "Lane") in view of Lau, *et al.*, Science 294:858-862 (2001)(hereinafter "Lau").

Minimally, a *prima facie* showing of obviousness under § 2143 of the Manual of Patent Examining Procedure (MPEP) requires that a reference or combination of references teach or suggest all of the claim limitations. While not acquiescing that these references meet the other requirements for establishing obviousness, Applicants respectfully submit that the combination of Ledford, Lane, and Lau fails to teach or suggest each of the elements of the instant claims.

Claims 32 and 57 and the claims depending therefrom recite at least the following elements and limitations:

- Forming an unlabeled* RNA detection structure comprising a microRNA and an unlabeled probe, the unlabeled probe comprising a portion that is complementary to the microRNA and a portion that forms a duplex[1] as a step in forming an unlabeled modified RNA detection structure; and
- disassociating said microRNA from the unlabeled probe; and detecting formation of said modified RNA detection structure after the disassociation has occurred.

[1] "unlabeled probe comprises a first region that is complementary to at least a portion of said microRNA wherein said portion of said microRNA comprises at least one of said 3' terminal end or said 5' terminal end of said microRNA, and a second region that is not complementary to said microRNA, wherein a first portion of said second region is complementary to a second portion of said second region, wherein said first portion and said second portion hybridize to each other to form a duplex when said unlabeled probe is hybridized to said microRNA"

*For clarity, and not in response to any Examiner argument and reserving the right to prosecute the original or similar claims in one or more future applications Claims 32 and 57 are amended herein to specify that the RNA detection structure and modified RNA detection structure are unlabeled. Dependent claims are similarly amended for consistency.

Ledford teaches the detection of genomic DNA using the two step Invader technology (see, *e.g.*, the title, and Figure 1). In the first step, a probe and an Invader oligonucleotide hybridize to the target DNA to form a first invasive complex, which is cleaved by the Cleavase cleavage agent (Fig. 1). The first invasive complex does not comprise an unlabeled probe comprising a portion that is complementary to a target nucleic acid and a portion that forms a duplex. Upon cleavage of the first invasive structure, a release flap from the first probe hybridizes to FRET-labeled hairpin probe (Fig. 1). The second invasive structure also does not comprise an unlabeled probe comprising a portion that is complementary to the target nucleic acid and a portion that forms a duplex.

While not acquiescing that Ledford teaches any other elements of the invention as claimed (*e.g.*, Ledford does not teach the formation of any structure comprising RNA, much less microRNA), Applicants point out that Ledford does not teach 1) an unlabeled probe comprising a portion that is complementary a target RNA and a portion that forms a duplex, or 2) the formation of an unlabeled RNA detection structure comprising an unlabeled probe comprising a portion that is complementary to the microRNA and a portion that forms a duplex, 3) formation of an unlabeled modified RNA detection structure, and 4) detection of an unlabeled modified RNA detection after the disassociation of the complex.

Lane does not cure these deficiencies. As noted by the Examiner, Lane teaches oligonucleotide probes having a secondary structure (Office Action page 5). However, Lane is directed to the detection of the presence of a complex between support-bound capture probe and a target nucleic acid. See, *e.g.*, Figures 5, 6, and 7, which pertain to measuring the amount of material bound to the capture probes. Lane does not teach or

suggest detection of the formation of a modified detection complex after the disassociation of the complex.

Furthermore, as the Examiner has noted, Lane expressly teaches that the duplex region of the probe stabilizes that specific region of the capture moiety and thereby favors formation of a target probe duplex (Office action page 5-6). Lane goes further than that, specifying that "the target-complementary region will be selected to ensure that target strands form stable duplexes with the capture moiety" (col. 6, lines 25-27, emphasis added). Thus, Lane expressly teaches *away* from disassociating the target nucleic acid from the probe. Nowhere does Lane teach detection of an unlabeled detection complex *after the disassociation* of the complex.

Lau discloses microRNAs in general but does not cure the deficiencies of Ledford and Lane with respect to the claimed embodiments of the present invention.

While Applicants do not acquiesce that the other elements necessary for establishing prima facie obviousness have been met, Applicants submit that the combination of Ledford, Lane and Lau does not teach or suggest all the limitations of Claims 32, 34, 35, 37-41, 48-54, 60, 61, 63-65, 72-74, 76, 77, 81 and 82, and the cited art therefore fails to establish prima facie obviousness. Applicants respectfully request that this rejection be removed.

3-5. Claims 33, 36, 44-47, 58, 59, and 62, and 68-71 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ledford, in view of Lane and in view of Lau, further in view of Morris.

Claims 42, 43, 53, 66, 67, and 77 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ledford in view of Lau and in view of Lane, further in view of Marras.

Claims 55, 56, 79 and 80 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ledford in view of Lau and in view of Lane, in further view of Hyidig-Nielsin.

For the reasons recited above, Applicants submit that the combination of Ledford, Lane and Lau fails teach or suggest detection of a microRNA using an unlabeled probe having the features recited in Claims 32 and 57, from which each of the above recited

claims depend. In particular, the combination of Ledford, Lane and Lau fails to teach formation of an unlabeled RNA detection structure comprising an unlabeled probe comprising a portion that is complementary to the microRNA and a portion that forms a duplex, formation of an unlabeled modified RNA detection structure, or detection of an unlabeled modified RNA detection after the disassociation of the complex.

Combination of these references with any of, Morris, Marris, or Hydig-Nielsin, or fails to cure these deficiencies, and the cited art therefore fails to establish prima facie obviousness. Applicants respectfully request that each of these rejections be removed.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that all grounds for rejection have been addressed and Applicant's claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourages the Examiner to call the undersigned collect at (608) 218-6900.

Dated: May 7, 2008

/Mary Ann D. Brow/
Mary Ann D. Brow
Registration No. 42,363

CASIMIR JONES, S.C.
440 Science Dr., Suite 203
Madison, WI, 53711
608-218-6900